

cell or tumor vasculature; the second region has coagulation-promoting activity or is a binding region for a coagulation factor. The disclosed bispecific binding ligand may be a bispecific (monoclonal) antibody, or the two ligands may be connected by a (selectively cleavable) covalent bond, a chemical linking agent, an avidin-biotin linkage, and the like. The target of the first binding region can be a cytokine-inducible component, and the cytokine can be released in response to a leukocyte-activating antibody; this may be a bispecific antibody which crosslinks activated leukocytes with tumor cells.

The phrase "cyclooxygenase-2 inhibitor" or "COX-2 inhibitor" or "cyclooxygenase-II inhibitor" includes agents that specifically inhibit a class of enzymes, cyclooxygenase-2, with less significant inhibition of cyclooxygenase-1. Preferably, it includes compounds which have a cyclooxygenase-2 IC<sub>50</sub> of less than about 0.2  $\mu$ M, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC<sub>50</sub> of greater than about 1  $\mu$ M, and more preferably of greater than 10  $\mu$ M.

Studies indicate that prostaglandins synthesized by cyclooxygenases play a critical role in the initiation and promotion of cancer. Moreover, COX-2 is overexpressed in neoplastic lesions of the colon, breast, lung, prostate, esophagus, pancreas, intestine, cervix, ovaries, urinary bladder, and head & neck. In

several in vitro and animal models, COX-2 inhibitors have inhibited tumor growth and metastasis.

In addition to cancers *per se*, COX-2 is also expressed in the angiogenic vasculature within and adjacent to hyperplastic and neoplastic lesions indicating that COX-2 plays a role in angiogenesis. In both the mouse and rat, COX-2 inhibitors markedly inhibited bFGF-induced neovascularization. The utility of COX-2 inhibitors as chemopreventive, antiangiogenic and chemotherapeutic agents is described in the literature (Koki et al., Potential utility of COX-2 inhibitors in chemoprevention and chemotherapy. Exp. Opin. Invest. Drugs (1999) 8(10) pp. 1623-1638, hereby incorporated by reference). Amplification and/or overexpression of HER-2/*neu* (ErbB2) occurs in 20-30% of human breast and ovarian cancers as well as in 5-15% of gastric and esophageal cancers and is associated with poor prognosis. Additionally, it has been recently discovered in vitro that COX-2 expression is upregulated in cells overexpressing the HER-2/*neu* oncogene. (Subbaramaiah et al., Increased expression of cyclooxygenase-2 in HER-2/*neu*-overexpressing breast cancer. Cancer Research (submitted 1999), hereby incorporated by reference). In this study, markedly increased levels of PGE<sub>2</sub> production, COX-2 protein and mRNA were detected in HER-2/*neu* transformed mammary epithelial cells compared to a non-transformed partner cell line. Products of COX-2 activity, i.e., prostaglandins, stimulate proliferation, increase invasiveness of malignant cells, and enhance the production of vascular endothelial growth factor, which promotes angiogenesis. Further, HER-2/*neu* induces the

production of angiogenic factors such as vascular endothelial growth factor.

Consequently, the administration of a COX-2 inhibitor in combination with an anti HER-2/neu antibodies such as trastuzumab (Herceptin®) and other therapies directed at inhibiting HER-2/neu is contemplated to treat cancers in which HER-2/neu is overexpressed.

Also, it is contemplated that COX-2 levels are elevated in tumors with amplification and/or overexpression of other oncogenes including but not limited to c-myc, N-myc, L-myc, K-ras, H-ras, N-ras. Products of COX-2 activity stimulate cell proliferation, inhibit immune surveillance, increase invasiveness of malignant cells, and promote angiogenesis. Consequently, the administration of a COX-2 inhibitor in combination with an agent or agents that inhibits or suppresses oncogenes is contemplated to prevent or treat cancers in which oncogenes are overexpressed.

Accordingly, there is a need for a method of treating or preventing cancer in a patient that overexpresses COX-2 and/or an oncogene. Methods for the production of anti- ErbB2 antibodies are described in WO 99/31140.

Specific COX-2 inhibitors are useful for the treatment of cancer (WO98/16227) and in several animal models reduce angiogenesis driven by various growth factors (WO98/22101). Anti-angiogenesis was achieved with a COX-2 inhibitor in rats implanted with bFGF, vascular endothelium growth factor (VEGF) or carrageenan, proteins with well-known angiogenic properties. (Masferrer, et al., 89<sup>th</sup> Annual Meeting of